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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,973	HANKE, PAUL D.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-20* is/are pending in the application.

4a) Of the above claim(s) *9-11 and 14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-8,12,13,19 and 20* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 25, 2004 has been entered.

The amendment filed February 25, 2004 amending the specification to clarify the text, amending claims 1, 2, 19 and canceling claims 21-23 has been entered.

Claims 1-3 and 5-20 are pending. Claims 9-11 and 14-18 are withdrawn.

It is noted that the statement regarding the biological Deposit of *E. coli* NRRL B-30293 is given in Remarks of August 22, 2003 (paragraph bridging pages 28-29). However, the date of Deposit is indicated as May 30, 2000 where it appears to be May 12, 2000. Applicant is required to submit a substitute statement with the correct date of the deposit.

Drawings

The corrected drawings of Figures 3A-3C and Figure 5 were received on February 25, 2004. These drawings are acceptable.

The corrected drawing of Figure 4 was received on February 25, 2004. This drawing is not acceptable. Figure 4 contains an inner box referring to "pyc ATCC 21253 IN E. coli" and "pyc NRRL B-11474 IN NRRL B-11474". It is unclear what information other than the information contained in the legend this box is supposed to convey.

Specification

The description of figure 2 has been amended. While it recites deposit numbers ATCC 21253 and NRRL B-11474, it is preferable to refer to *Corynebacterium glutamicum* ATCC 21253 and *Corynebacterium glutamicum* NRRL B-11474.

Furthermore, in several instances the date of the deposit of *E. coli* NRRL B-30293 is indicated as May 30, 2000 where it appears to be May 12, 2000 (e.g., page 6).

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-8, 12, 13, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA encoding SEQ ID NO:2, including SEQ ID NO:1, a DNA encoding a pyruvate carboxylase having an amino acid sequence that differs from SEQ ID NO:19 by at least one of the seven

specific mutations, said pyruvate carboxylase being desensitized to feedback inhibition by aspartic acid and a DNA at least 95 % identical to SEQ ID NO:1 encoding a pyruvate carboxylase having an amino acid sequence comprising all seven specified mutations in SEQ ID NO:19 said pyruvate carboxylase being desensitized to feedback inhibition by aspartic acid, does not reasonably provide enablement for a DNA at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase that is desensitized to feedback inhibition by aspartic acid, said mutant pyruvate carboxylase having an amino acid sequence containing at least one of the seven specific mutations or comprising SEQ ID NOs:6 or 18. It does not reasonably provide enablement for a DNA at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase that is desensitized to feedback inhibition by aspartic acid, said mutant pyruvate carboxylase comprising SEQ ID NOs:8, 10, 12, 14 or 16, i.e. having an amino acid sequence containing a mutation at any position. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is

required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claim 1, with dependent claims 5-8, 12 and 13, is directed to a nucleic acid at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase that is desensitized to feedback inhibition by aspartic acid, said mutant pyruvate carboxylase having an amino acid sequence containing at least one mutation selected from the group consisting of seven specific mutations in SEQ ID NO:19.

The specification teaches a DNA of SEQ ID NO:1 that encodes a mutant pyruvate carboxylase of SEQ ID NO:2 having seven specific mutations relative to the wild-type sequence of SEQ ID NO:19. The specification does not teach any DNA sequence at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase with the requisite property comprising only one of the seven specified mutations and additional mutations at any positions. Further, it fails to provide information regarding other combinations of substitute amino acids that would result in a mutant with the requisite characteristics. The art discloses a DNA that encodes a pyruvate carboxylase having the amino acid sequence that differs from SEQ ID NO:19 by replacement of methionine at position 1 with a valine, said enzyme apparently not being feed-back resistant (Sinskey et al. Database Genseq, accession AAB01436, sequence alignment). While there is a great number of possible mutants, it is *a priori*

unpredictable as to which mutant will exhibit the claimed property. Therefore, the breadth of these claims is much larger than the scope enabled by the specification. With regard to claims 19 and 20, SEQ ID NO: 6 is a fragment of SEQ ID NO:2 corresponding to residues 164-176. Therefore, SEQ ID NO: 6 comprises a single mutation at position corresponding to position 153 in SEQ ID NO: 19. SEQ ID NO: 18 is a fragment of SEQ ID NO:2 corresponding to residues 1-18. Therefore, SEQ ID NO: 18 comprises a single mutation at position corresponding to position 1 in SEQ ID NO: 19. SEQ ID NOs: 8, 10, 12, 14 and 16 comprise no mutations compared to SEQ ID NO:19.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of what changes in the amino acid sequence can be tolerated and result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of peptide mutants where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

The specification does not support the broad scope of the claims which encompass DNAs at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase with the requisite property comprising less than seven specified mutations and additional mutations at any positions because the specification does **not** establish: (A) regions of the protein structure which may be modified without

effecting the requisite pyruvate carboxylase activity; (B) the general tolerance of said pyruvate carboxylase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any pyruvate carboxylase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Therefore, one of ordinary skill would require guidance, such as information regarding the specific amino acid changes that would render a pyruvate carboxylase desensitized to feedback inhibition by aspartic acid, in order to make a DNA at least 95% identical to SEQ ID NO:1 encoding a mutant pyruvate carboxylase with the requisite property and comprising less than seven specified mutations in SEQ ID NO:19 in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-8, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, with dependent claims 5-8, 12, 13, recites "pyruvate carboxylase enzyme contains at least one mutation to SEQ ID NO:19 which desensitizes said pyruvate carboxylase enzyme to feedback inhibition by aspartic acid". Thus, the claim

does not define the function of the enzyme as being feedback resistant but only defines the function of the mutation. The enzyme may contain said mutation and not be desensitized to feedback inhibition by aspartic acid. Therefore, the metes and bounds of the claim are unascertainable.

Claim 2, with dependent claims 5-8, 12, 13, recites a nucleotide sequence encoding the amino acid sequence encoded by the DNA contained in Deposit Number NRRL B-30293". The clam is unclear because the DNA contained in E. coli NRRL B-30293 encodes various amino acid sequences not necessarily that of a feedback resistant pyruvate carboxylase. Amending the claims to recite "encoded by the DNA plasmid encoding feedback resistant pyruvate carboxylase", for example, is suggested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5-8, 12, 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Sinskey et al.

Sinskey et al. (WO 00/39305, July 6, 2000, Genseq accession AAB01436, *supra*) teach a DNA encoding a pyruvate carboxylase having an amino acid

sequence that differs from SEQ ID NO :19 by replacement a methionine at position 1 with a valine (Figure 1), a vector and a host cell comprising thereof. While it contains one of the mutations, the enzyme is not feedback resistant. It anticipates claims 1, 5-8, 12, 13 because the claimed enzyme does not need to be feed back resistant as explained in the 112, 2nd paragraph, rejection.

Allowable Subject Matter

Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Response to Arguments

Applicant's arguments filed February 25, 2004 have been fully considered but they are not persuasive.

Applicant argues that amending claim 1 to recite "at least 95 % to SEQ ID NO: 1" should obviate the 112, 1st paragraph, rejection. The rejection above explains that applicant did not show that less than seven specified mutations are sufficient to impart the requisite property to SEQ ID NO:19. The specification provides no indication that any one of the seven mutations is sufficient. The art, *supra,* teaches a pyruvate carboxylase mutated at position 1 that does not exhibit the requisite property.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan

producing variants as claimed by applicants (i.e., encoding a mutant pyruvate carboxylase that is desensitized to feedback inhibition by aspartic acid) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting pyruvate carboxylase activity and feedback inhibition by aspartic acid; (B) the general tolerance of pyruvate carboxylases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any pyruvate carboxylase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-

272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
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Art Unit 1652

April 2, 2004